REMARKS

Claims 1 to 29 are pending in this application. Claims 11 to 28 stand rejected. Claims 1 to 4, 9, 11 to 25, 28, and 29 are newly rejected and claims 5 to 8 and 10 are newly objected to. Applicants are herein amending claims 1, 9, 11, 13, 16, 18, 19, 25, 28, and 29. Applicants request reconsideration of the rejections in light of the amendments and following remarks.

Summary of Rejections

Claims 11 to 28 stand rejected as follows:

- claims 11 to 28 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled;
- claims 23 and 24 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite;
- claims 11 to 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 27 to 55 of US 10/820,215; and
- claims 11 to 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1 to 95 and 104 to 108 of US 10/961,871.

Claims 1 to 4, 9, 11 to 25, 28, and 29 are newly rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 5 to 8 and 10 are newly objected to as being dependent upon a rejected base claim, but are otherwise allowable. Applicants acknowledge with appreciation that the remaining rejections have been withdrawn.

Amendments to Claims

Applicants are herein amending claims 1, 9, 11, 13, 16, 18, 19, 25, 28, and 29 to correct obvious typographical errors:

- In claims 9 and 28, applicants are removing an extraneous hyphen in the name of the compound listed at e).

- In claims 1, 11, 13, 16, 18, 19, 25, and 29, applicants are correcting the carbon number in the alkylaryl moiety in R_6, R_7 and R_8, where incorrect.
- In claim 11, applicants are correcting the spelling of the word "and" in "diabetic and organ complications."
- In claim 29, applicants are correcting the superscript on C_{14} in R_1.

Applicants submit that no new matter is introduced by the amendments to the claims and that they are fully supported by the specification, as originally filed. For example, the definition of alkylaryl provided in the specification on page 7, lines 12 to 20 and lines 24 to 29, where the number of carbon atoms is 6 (from 1+5) to **21** (from 8+13):

> Aryl, as used herein, refers to an aromatic 5- to **13**-membered mono- or bi-carbocyclic ring such as phenyl or napthyl. Preferably, groups containing aryl moieties are monocyclic having 5 to 7 carbon atoms in the ring. Heteroaryl means an aromatic 5- to 13-membered carbon containing mono- or bi- cyclic ring having one to five heteroatoms which independently may be nitrogen, oxygen or sulfur. Preferably, groups containing heteroaryl moieties are monocyclic having 5 to 7 members in the ring where one to two of the ring members are selected independently from nitrogen, oxygen or sulfur. Groups containing aryl or heteroaryl moieties may optionally be substituted as defined below or unsubstituted.
>
> Alkylaryl, as used herein refers to the group -R-Ar where Ar is aryl as defined above and R is an alkyl moiety having 1 to **8**, preferably 1 to 6, and more preferably 1 to 4 carbon atoms. Examples of alkylaryl groups include benzyl, phenethyl, 3-phenylpropyl, and 4-phenyl butyl. Alkylheteroaryl, as used herein refers to the group -R-hetAr where hetAr is heteroaryl as defined above and R is an alkyl moiety having 1 to 8, preferably 1 to 6, and more preferably 1 to 4 carbon atoms.

Applicants request the entry of the amendment under 37 C.F.R. § 1.116(b) because the amendments to the claims either cancel claims, comply with requirements of form expressly set forth in a previous Office Action, or present the rejected claims in better form for consideration on appeal.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 11 to 28 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. More specifically, the Office maintains that it is not sufficient to support enablement of claims 11 to 28 by establishing a nexus between NMDA antagonists and the treatment of the diseases and/or disorders listed in the claims. The Office further urges that treatment does not imply prevention. Applicants traverse the rejection.

As previously explained, with respect to the prevention of disorders, no evidence has been presented that there is any reason to believe that a skilled artisan would doubt that the compounds of the invention would not be useful in preventing opiate tolerance, especially in light of the fact that NMDA receptor antagonists are known to prevent the opiate analgesia tolerance. See, for example, the Trujillo abstract (previously provided). Contrary to the allegations in the latest action, this abstract indicates that a decade of research establishes that "NMDA receptor antagonists have the ability to inhibit opiate tolerance," even if the exact mode of action is not known. Furthermore, medical professionals have means to measure tolerance to opiate analgesia and would have no difficulty administering the compounds of the invention to effect the desired result, *i.e.*, prevention of the tolerance. No other evidence has been presented that establishes that a skilled artisan would doubt the use of the compounds of the invention, which are NMDA receptor antagonists, would not be useful in the treatment of the listed diseases and conditions.

Applicants submit that the method of treatment claims meet the enablement requirement under 35 U.S.C. § 112, first paragraph. With the exception of cerebral ischemia, it appears that the Office is challenging that there is a correlation between antagonists of the NMDA receptor and the treatment of the various diseases and conditions claimed. As applicants explained on page 14, line 8 to page 15, line 11, the present invention provides methods for treating conditions associated with glutamate abnormalities, *i.e.,* conditions produced by a disease or a disorder in which glutamate, typically in increased amounts, is implicated as a contributing factor. The Office has provided no evidence that any of the listed conditions would not be expected to be treated by the compounds of the invention. A

rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonably based upon the probative evidence. (citations omitted).

Applicant previously submitted a number of review articles that show that there is recognized correlation between antagonism at the NMDA receptors and the specified diseases and conditions set forth in the claims:

- Wood PL.
  The NMDA receptor complex: a long and winding road to therapeutics.
  Drugs. 2005 Mar;8(3):229-35. Review.

- Heresco-Levy U.
  Glutamatergic neurotransmission modulators as emerging new drugs for schizophrenia.
  Expert Opin Emerg Drugs. 2005 Nov;10(4):827-44. Review.

- Bergink V, van Megen HJ, Westenberg HG.
  Glutamate and anxiety.
  Eur Neuropsychopharmacol. 2004 May;14(3):175-83. Review.

- Parsons CG.
  NMDA receptors as targets for drug action in neuropathic pain.
  Eur J Pharmacol. 2001 Oct 19;429(1-3):71-8. Review.

- Brown DG, Krupp JJ.
  N-methyl-D-aspartate receptor (NMDA) antagonists as potential pain therapeutics.
  Curr Top Med Chem. 2006;6(8):749-70

- McCulloch J.
  Excitatory amino acid antagonists and their potential for the treatment of ischaemic brain damage in man.
  Br J Clin Pharmacol. 1992 Aug;34(2):106-14. Review.

Applicants have tested compounds of the invention, which are NMDA receptor antagonists, in the art-recognized preclinical *in vivo* prostaglandin E_2-induced thermal hypersensitivity test. If the prior art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted by the Office as correlating unless the Office has evidence that the model does not correlate. Even with such evidence, the Office must weight the evidence for and against such correlation and determine whether a skilled artisan would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Applicants submit that the Office has not met this burden.

Accordingly, applicants submit that claims 11 to 28 meet the enablement requirement under 35 U.S.C. § 112, second paragraph, and therefore request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 23 and 24 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1 to 4, 9, 11 to 25, 28, and 29 are *newly* rejected. Applicants traverse the rejection.

Claims 23 and 24

Claims 23 and 24 stand rejected for using the phrase "pain relieving agent." Applicants traverse the rejection because a skilled artisan would have no difficulty understanding the meaning of the phrase. Furthermore, on page 19, lines 27 to page 21, line 21, applicants have provided numerous specific examples of pain relieving agents, leaving no doubt with the skilled artisan to the metes and bounds of the invention with respect to the pain relieving agents.

Claims 1 to 4 and 11 to 25

Claims 1 to 4 and 11 to 25 are *newly* rejected for ambiguity with respect to the alkylaryl group in R_6 (a ~~C_6 to C_2~~ $\underline{C_6 \text{ to } C_{21}}$ alkylaryl group having 5 to 13 carbon atoms in the aryl moiety). Applicants are herein amending claims 1, 11, 13, 16, 18, 19, 25, and 29 to correct the typographical error with respect to the alkylaryl group in R_6. Applicants submit that the amendment to claims 1, 11, 13, 16, 18, 19, 25, and 29 renders moot the rejection of claims 1 to 4 and 11 to 25. If such is not the case, applicants submit that the rejection minimally should not be made final because no amendment precipitated the rejection, as alleged by the Office.

Claims 1 to 4, 11 to 25, and 29

Claims 1 to 4, 11 to 25, and 29 are also *newly* rejected as allegedly lack of antecedent basis for "5 to 13 carbon atoms in the aryl moiety." Applicants are herein amending claims 1, 11, 13, 16, 18, 19, 25, and 29 to correct the typographical error with respect to the alkylaryl group in R_6, R_7, and R_8, as needed. Applicants submit that the amendment to claims 1, 11, 13, 16, 18, 19, 25, and 29 renders moot the rejection of claims 1 to 4, 11 to 25, and 29. If such is not the case, applicants submit that the rejection minimally should not be made final because no amendment precipitated the rejection, as alleged by the Office.

Claims 9 and 28

Claims 9 and 28 are *newly* rejected as allegedly ambiguous with respect to species e). Applicants are herein amending claims 9 and 28 to correct the typographical error with respect to the extraneous hyphen in the name of the compound. Applicants submit that the amendment to claim 9 and 28 renders moot the rejection of the claim. If such is not the case, applicants submit that the rejection minimally should not be made final because no amendment precipitated the rejection, as alleged by the Office.

Claims 11 and 12

Claims 11 and 12 are *newly* rejected as allegedly ambiguous with respect to the phrase "diabetic end organ complications." Applicants are herein amending claim 11 to correct the typographical error with respect to "end," which should read "and." Applicants submit that the amendment to claim 11 renders moot the rejection of the claims 11 and 12. If such is not the case, applicants submit that the rejection minimally should not be made final because no amendment precipitated the rejection, as alleged by the Office.

Claim 29

Claim 29 is *newly* rejected as allegedly ambiguous with respect to the "C14 aroyl" in R_1 and "C12" in R_7 and R_8. Applicants are herein amending claim 29 to correct the typographical error with respect to the superscripted "14" and to address the issue with respect to "C12," respectively. Applicants submit that the amendment to claim 29 renders moot the rejections of this claim. If such is not the case, applicants submit that the rejection minimally should not be made final because no amendment precipitated the rejection, as alleged by the Office.

Applicants submit that claims 1 to 4, 9, 11 to 25, 28, and 29, as amended, meet the definiteness requirement under 35 U.S.C. § 112, second paragraph, and therefore request withdrawal of the rejection.

Obviousness-type Double Patenting Rejections

Claims 11 to 28 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 27 to 55 of US 10/820,215. Also, claims 11 to 28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1 to 95 and 104 to 108 of US 10/961,871.

Applicants request that these provisional rejections be held in abeyance until the identification of otherwise allowable subject matter.

Objections to Claims

Claims 5 to 8 and 10 are newly objected to as being dependent upon a rejected base claim, but are otherwise allowable. Applicants request reconsideration of the objection to the claims in light of the amendments to the claims and remarks.

Conclusions

Applicants request:

(1) entry of the amendments to the claims;

(2) reconsideration and withdrawal of the rejections of the claims 1 to 4, 9, and 11 to 29;

(3) reconsideration and withdrawal of the objections to claims 5 to 8 and 10;

(4) reconsideration and withdrawal of the finality of the rejection of the claims; and

(5) allowance of claims 1 to 29.

If the Examiner is of a contrary view, the Examiner is requested to contact the undersigned attorney at (404) 459-5642.

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/Wendy A. Choi/
Wendy A. Choi
Registration No. 36,697

WOODCOCK WASHBURN LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439